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Ambient Water Quality Criteria Hexachlorocyclohexane

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HEXACHLOROCYCLOHEXANE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for hexachlorocyclohexane. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in, ...

KEYWORDS: *Water quality, *Toxicology, *Toxic substances, *Water pollution effects(Humans), *Cyclohexane/hexachloro.

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CRITERION DOCUMENT

HEXACHLOROCYCLOHEXANE

CRITERIA

Aquatic Life

Lindane

For lindane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.21 µg/l as a 24-hour average and the concentration should not exceed 2.9 µg/l at any time.

For saltwater aquatic life, no criterion for lindane can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

BHC

For freshwater aquatic life, no criterion for a mixture of isomers of BHC can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for a mixture of isomers of BHC can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to α-HCH, β-HCH, and γ-HCH through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of α-HCH, β-HCH, and γ-HCH estimated to result in additional

lifetime cancer risks ranging from no additional risk to an aal tional risk of 1 in 100,000 are presented in the Criterion Foddi- mulation section of this document. The Agency is consideringr- setting criteria at an interim target risk level in the range 10-5, 10-6, or 10-7 with corresponding criteria as follows: of

Isomer	Criteria (ng/l) at the following risk levels		
	10^{-5}	10^{-6}	10^{-7}
α-HCH	16	1.6	0.16
β-HCH	28	2.8	0.28
γ-HCH	54	5.4	0.54
t-HCH	21	2.1	0.21

There is insufficient data to establish criteria for the δ and ϵ isomers of HCH.

Introduction

Hexachlorocyclohexane is a broad spectrum insecticide of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. It consists of a mixture of five configurational isomers and was introduced in 1942 as a contact insecticide under the trade names BHC, benzene hexachloride, and 666. Since its introduction, both the uses and production volume of technical grade BHC have undergone dramatic changes as a result of the discovery that virtually all of the insecticidal activity of BHC resides with its gamma isomer. By voluntary action, the principal domestic producer of technical grade BHC requested cancellations of its BHC registrations on September 1, 1976. As of July 21, 1978 all registrants of pesticide products containing BHC voluntarily cancelled their registrations or switched their former BHC products to lindane formulations. On the other hand, significant commercial use of the purified gamma isomer of BHC (lindane) continues. As of January 17, 1977, there were 557 Federal registrations for pesticide products containing lindane and 87 formerly State-registered products containing lindane for which Federal registration has been requested.

Hexachlorocyclohexane, commonly referred to as BHC or benzene hexachloride, is a brownish-to-white crystalline solid with a phosgene-like odor, a molecular formula of $C_6H_6Cl_6$, a molecular weight of 290.0, a melting point of 65°C, and a solubility in water of 10 to 32 mg/l (Hardie, 1972; Cristensen, 1976; Matsumura, 1975). BHC is the common

name approved by the International Standards Organization for the mixed configurational isomers of 1,2,3,4,5,6-hexachlorocyclohexane, although the terms BHC and benzene hexachloride are misnomers for this aliphatic compound and should not be confused with aromatic compounds of similar structure, such as the aromatic compound hexachlorobenzene (Int. Agency Res. Cancer, 1974). Lindane is the common name approved by the International Standards Organization for the gamma-isomer of 1,2,3,4,5,6-hexachlorocyclohexane. BHC is synthesized by the direct action of chlorine on benzene in the presence of ultraviolet light (Hardie, 1972).

Technical grade BHC contains the hexachlorocyclohexane isomers in the following ranges: alpha-isomer, 55 to 70 percent; beta-isomer, 6 to 8 percent; gamma-isomer, 10 to 18 percent; delta-isomer, 3 to 4 percent; epsilon-isomer, trace amounts (Hardie, 1972). The actual content of the isomers in technical grade BHC varies depending on the manufacturing conditions.

In addition to the hexachlorocyclohexane isomers, technical grade BHC may contain varying quantities (three to five percent) of other chlorinated derivatives of cyclohexane, primarily heptachlorocyclohexane and octachlorocyclohexane.

Technical grade BHC is available in various formulations as wettable powders, granules, dusts, and emulsifiable concentrates and can be used as a stomach and contact poison for a wide variety of insect pests and animal parasites. Since the gamma-isomer (lindane) has been shown to be the insecticidally active ingredient in technical grade BHC (Hardie,

1972), technical grade BHC now has limited use commercially except as the raw material from which the purified gamma-isomer is extracted by a process of selective crystallization.

Technical grade lindane is composed of 99 to 100 percent pure gamma-BHC isomer and is available in the form of emulsifiable concentrates, wettable powders, dusts, crystals, and solids for smoke generators and thermal vaporizers.

The physical properties of the purified BHC isomers are presented in Table 1.

TABLE 1

Physical properties of BHC isomers
(Ulmann, 1972; Hardie, 1972)

BHC isomer	Melting point (deg.C)	Vapor pressure (mm Hg at 50 deg.C)	Water solubility (mg/l)	Solubility in relatively non polar solvent (g/100 g ether at 20 deg.C)
alpha	158	0.00087	10	6.2
beta	312	0.000014	5	1.8
gamma	112.5	0.0008	10	20.8
delta	138	---	10	35.4

The isomers of BHC are not susceptible to photolysis or strong acids but are, with the exception of the beta isomer, dehydrochlorinated by alkalies to form primarily 1,2,4-trichlorobenzene (Hardie, 1972). Lindane has been shown to be slowly degraded (ten percent degradation after six weeks) by soil microorganisms (Mathur and Saha, 1975) and is capable of isomerization to alpha and/or delta BHC by microorgamisms and plants (Matsumura, et al. 1976; Newland, et al. 1969; and Steinwandter, 1976).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Hexachlorocyclohexane is a member of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. It is manufactured by the chlorination of benzene and is commonly called BHC or benzene hexachloride. Hexachlorocyclohexane is an aliphatic compound and should not be confused with aromatic compounds of a similar structure. The aromatic compounds are also called BHC, benzene hexachloride or hexachlorobenzene, so caution is advised when reading reports on these chemicals.

The International Standards Organization has approved the common name BHC for the mixed configurational isomers of 1,2,3,4,5,6-hexachlorocyclohexane. Technical grade BHC contains five hexachlorocyclohexane isomers. They are alpha (55 to 70 percent), beta (6 to 8 percent), gamma (10 to 18 percent), delta (3 to 4 percent) and epsilion (trace). The gamma isomer is usually considered to be the most toxic, and preparations which contain at least 99 percent of the gamma isomer are called lindane.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The majority of the effects data were for the gamma isomer (lindane). A criterion was developed for this compound. There are additional data for technical BHC, which contains varying amounts of the gamma isomer and the alpha isomer. The data for these compounds are included in the Tables but are insufficient for criteria development.

Acute Toxicity

Twenty-five of the 31 acute toxicity test results reported in Table 1 are for lindane and represent 16 species of fish. The remaining 6 test results are for BHC. Most are 96-hour static tests and all have been based on calculated toxicant concentrations. For comparative purposes, these data have been adjusted using the Guidelines.

The adjusted values for lindane range from 1 to 83 µg/l for brown trout and goldfish, respectively. These values represent an interspecific difference in response to lindane exposure. Generally, the warmwater fish appear to be more tolerant of lindane exposure than the coldwater salmonids.

The 96-hour LC50 values for BHC are much higher than those for lindane. The difference cannot be explained by simple ratio of the lindane content in the BHC to pure lindane. For example, Henderson, et al. (1959) based their LC50 values for BHC on the gamma isomer content and found that the gamma isomer in BHC was approximately 244 times less toxic to the fathead minnow in soft water than the gamma isomer tested alone. In fact, the BHC concentrations were so high that precipitates were observed.

In addition, they determined a concentration of 0.1 mg/l of lindane alone caused 100 percent mortality of fathead minnows in 24 hours. When 3.2 mg/l of technical BHC, a concentration that caused no mortality, and 0.1 mg/l lindane were added to the same tank, no mortality occurred within 96 hours. They concluded that the other BHC isomers either had reduced the solubility of the gamma isomer (lindane) or had produced an antagonistic effect reducing its toxicity.

When the geometric mean of the lindane data is divided by the sensitivity factor (3.9), the Final Fish Acute Value is 6.9 µg/l. Because the Final Fish Acute Value is lower than 95 percent (15 of 16 fish species) of the acute data, adjustment factors from the Guidelines are appropriate. The Final Fish Acute Value for BHC is 740 µg/l.

Eleven toxicity tests with lindane and eight species of invertebrate species are reported in Table 2. Three toxicological groups can be formed from the data. The three cladoceran species are the most resistant organisms tested. The LC50 concentrations ranged from 390 to 745 µg/l or about 10 to 100 times higher than the LC50 concentrations for the next group. The crustaceans, represented by the sowbugs and scud, are generally the most sensitive species tested. With these animals, the LC50 value ranged from 8 to 41 µg/l. The last group, represented by two insect species, shows a wide range in LC50 values. The most sensitive species of all the tested invertebrate species was the stonefly with a LC50 of 4 µg/l. The other insect, a chironomid, had a LC50 of 175 µg/l which is between the cladoceran and crustacean toxic concentrations.

The geometric mean of the adjusted values for lindane is 62 µg/l. When this value is divided by the sensitivity factor (21), the resulting Final Invertebrate Acute Value, 2.9 µg/l, is lower than any of the reported acute values. The cladoceran and crustacean LC50 values are interspecifically consistent, whereas the insect data show a substantial divergence. However, the stonefly has been shown in studies with other pesticides to be a sensitive indicator, so the acute value reported here may be close to a minimum for insects. Because the adjusted acute value is lower than the reported values, it should be protective on an acute exposure basis.

Since the Final Invertebrate Acute Value for lindane (2.9 µg/l) is lower than the comparable value for fish (6.9 µg/l), the former value becomes the Final Acute Value for lindane.

Only one chronic test with fish was found. The geometric mean of the chronic values for the fathead minnow is 14.6 µg/l. Interpretation of this value requires a re-examination of the fish acute data. The geometric mean of the fathead minnow acute concentrations is about 37 µg/l. This compares favorably with the overall geometric mean of 27 µg/l for all fish acute concentrations. Because of the similarity, it is appropriate to consider the fathead minnow as an average fish with regard to lindane toxicity. The adjustment of the geometric mean of 14.6 µg/l by the sensitivity factor (6.7) provides a Final Fish Chronic Value for lindane of 2.2 µg/l which should give protection for 95 percent of the species. However, one acute value (brown trout LC50 = 1 µg/l) is lower than the Final Fish Chronic Value, but this value is much lower than those for three other salmonids.

Chronic data are available for three invertebrate species. Fortunately, the three species are members of the three classes already described in the invertebrate acute section. Longer exposure resulted in a substantial decrease in the effect concentration for the cladoceran, Daphnia magna, (28x) and the chironomid, Chironomus tentans, (53x) but little decrease for the scud, Gammarus fasciatus, (1.6x).

The geometric mean of the chronic values is 6.6 µg/l. When this value is adjusted with the sensitivity factor (5.1), the resulting Final Invertebrate Chronic value for lindane is 1.3 µg/l.

The substantial decrease in effect concentrations between acute and chronic invertebrate exposures for 2 of the 3 species presents a concern for the safety of the final chronic value for other untested species. If the acute to chronic ratio for other cladocerans or insects is consistent, some untested species may not be protected at 1.3 µg/l, since the Final Invertebrate Acute Value is 2.9 µg/l.

Plant Effects

The effect of hexachlorocyclohexane on plants must be estimated from only one report (Krishnakumari, 1977). Growth inhibition of an alga was reported at 500 to 5,000 µg/l depending on the isomer used in the exposures. The alpha isomer was the most toxic at 500 µg/l while the more commonly used gamma isomer (lindane) inhibited growth at 1,000 µg/l. The gamma isomer effect concentration is about 770 times higher than the invertebrate chronic value, so the plants should be protected.

Residues

Bioconcentration factors (Table 6) include mean factors determined using data obtained from a small oligotrophic lentic ecosystem (a flooded limestone quarry), where the fate of introduced lindane and DDE was followed for one year (Hamelink and Waybrant, 1976). They reported average steady-state bioconcentration factors for lindane of 768 and 486 for whole bluegills and rainbow trout, respectively. They used mean concentration data from all thermal statra under summer water conditions to calculate their bluegill concentration factor. This value (768) was not used because the bluegill would probably stay above the thermocline. A bioconcentration factor (340) was calculated using their epilimnion lindane concentration data and is thought to reflect exposure conditions for the bluegills. Seventy percent of the lindane was evenly distributed in the epilimnion, and concentrations were relatively constant until fall turnover (destratification). After turnover, the lindane concentrations were similar throughout the water column. Their rainbow trout bioconcentration factor data were obtained under these conditions. The remaining bioconcentration factors (Table 6) are those of Macek, et al. (1976) and were obtained under laboratory conditions. These values are for muscle tissue in bluegill and brook trout and for eviscerated fathead minnows. Their bluegill muscle factor (35) is aproximately 10 times less than that calculated for whole bluegills (340). This difference is probably due to different lipid content.

The residue limit for consumers of aquatic life, established by the U.S. Food and Drug Administration (FDA) for lindane in domestic animal feed is 0.1 mg/kg, and was used to calculate the

Residue Limited Toxicant Concentration (RLTC). This value divided by the highest geometric mean bioconcentration factor for whole fish tissue of any species, 486, gives a RLTC of 0.00021 mg/kg or 0.21 µg/l. The lowest of the Final Fish Chronic Value (2.2 µg/l), Final Invertebrate Chronic Value (1.3 µg/l), Final Plant Value (1,000 µg/l), and the RLTC (0.21 µg/l) is used to determine the Final Chronic Value. For lindane, the Final Chronic Value is 0.21 µg/l.

Miscellaneous

Table 7 contains data on lindane, the alpha-isomer, and the commercial trade mixture BHC. The data support the earlier findings that lindane is the most toxic isomer of BHC. No data were found that would alter the lindane Final Chronic Value of 0.21 µg/l.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Lindane

Final Fish Acute Value = 6.9 µg/l

Final Invertebrate Acute Value = 2.9 µg/l

Final Acute Value = 2.9 µg/l

Final Fish Chronic Value = 2.2 µg/l

Final Invertebrate Chronic Value = 1.3 µg/l

Final Plant Value = 1,000 µg/l

Residue Limited Toxicant Concentration = 0.21 µg/l

Final Chronic Value = 0.21 µg/l

0.44 x Final Acute Value = 1.3 µg/l

BHC

Final Fish Acute Value = 740 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 740 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 1,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1,000 µg/l

0.44 x Final Acute Value = 330 µg/l

Lindane

The maximum concentration of lindane is the Final Acute Value of 2.9 µg/l and the 24-hour average concentration is the Final

Chronic Value of 0.21 µg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For lindane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.21 µg/l as a 24-hour average, and the concentration should not exceed 2.9 µg/l at any time.

BHC

No freshwater criterion can be derived for a mixture of isomers of BHC using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for hexachlorocyclohexane

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	S	U	Lindane	96	27	15	Macek & McAllister, 1970
Rainbow trout, Salmo gairdneri	S	U	Lindane (98%)	96	38	21	Katz, 1961
Brown trout, Salmo trutta	S	U	Lindane	96	2	1	Macek & McAllister, 1970
Brook trout, Salvelinus fontinalis	FT	U	Lindane	96	44.3	34	Macek, et al. 1976
Coho salmon, Oncorhynchus kisutch	FT	U	BHC	48	200	154	Velson & Alderdice, 1967
Coho salmon, Oncorhynchus kisutch	S	U	Lindane	96	41	22	Macek & McAllister, 1970
Coho salmon, Oncorhynchus kisutch	S	U	Lindane (100%)	96	50	27	Katz, 1961
Chinook salmon, Oncorhynchus tshawytscha	S	U	Lindane (100%)	96	40	22	Katz, 1961
Goldfish, Carassius auratus	S	U	Lindane	96	131	72	Macek & McAllister, 1970
Goldfish, Carassius auratus	S	U	Lindane (100%)	96	152	83	Henderson, et al. 1959
Goldfish, Carassius auratus	S	U	BHC tech (15.5% gamma isomer)	96	15,000	8,200	Henderson, et al. 1959
Carp, Cyprinus carpio	S	U	Lindane	96	90	49	Macek & McAllister, 1970
Fathead minnow, Pimephales promelas	S	U	Lindane	96	87	48	Macek & McAllister, 1970

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, Pimephales promelas	S	U	Lindane (100%)	96	62	34	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	Lindane (100%)	96	56	31	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	BHC tech (15.5% gamma isomer)	96	15,000	8,200	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	BHC tech (15.5% gamma isomer)	96	13,000	7,100	Henderson, et al. 1959
Black bullhead, Ictalurus melas	S	U	Lindane	96	64	35	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	S	U	Lindane	96	44	24	Macek & McAllister, 1970
Guppy, Poecilia reticulatus	S	U	Lindane (100%)	96	138	75	Henderson, et al. 1959
Guppy, Poecilia reticulatus	S	U	BHC tech (15.5% gamma isomer)	96	14,000	7,654	Henderson, et al. 1959
Mosquitofish, Gambusia affinis	S	U	Lindane	48	74	33	Culley & Ferguson, 1969
Bluegill, Lepomis macrochirus	S	U	Tech lindane	96	54	29	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S	U	Tech lindane	96	51	28	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S	U	Tech lindane	96	37	20	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S	U	Lindane	96	68	37	Macek & McAllister, 1970

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill, Lepomis macrochirus	S	U	Lindane (100%)	96	77	42	Henderson, et al. 1959
Bluegill, Lepomis macrochirus	S	U	BHC tech (15.5% gamma isomer)	96	5,100	2,788	Henderson, et al. 1959
Redear sunfish, Lepomis microlophus	S	U	Lindane	96	83	45	Macek & McAllister, 1970
Largemouth bass, Micropterus salmoides	S	U	Lindane	96	32	17	Macek & McAllister, 1970
Yellow perch, Perca flavescens	S	U	Lindane	96	68	37	Macek & McAllister, 1970

* S = static, FT = flow-through

** U = unmeasured

Geometric mean of adjusted values for lindane = 22 µg/l $\frac{27}{3.9}$ = 6.9 µg/l

BHC = 2,901 µg/l $\frac{2,901}{3.9}$ = 740 µg/l

Table 2. Freshwater invertebrate acute values for hexachlorocyclohexane

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Pond snail, Lymnaea stagnalis	S	M	Alpha HCH	48	1,200	568	Canton & Slooff, 1977
Cladoceran, Daphnia pulex	S	U	Lindane	48	460	390	Sanders & Cope, 1966
Cladoceran, Daphnia magna	S	U	Lindane	48	485	411	Macek, et al. 1976
Cladoceran, Simocephalus serralatus	S	U	Lindane	48	520	440	Sanders & Cope, 1966
Cladoceran, Simocephalus serralatus	S	U	Lindane	48	880	745	Sanders & Cope, 1966
Sowbug, Asellus brevicaudus	S	U	Lindane (99%)	96	10	8	Sanders, 1972
Scud, Gammarus lacustris	S	U	Lindane	96	48	41	Sanders, 1969
Scud, Gammarus fasciatus	S	U	Lindane	48	39	14	Macek, et al. 1976
Scud, Gammarus fasciatus	S	U	Lindane (99%)	96	10	8	Sanders, 1972
Scud, Gammarus fasciatus	S	U	Lindane (99%)	96	11	9	Sanders, 1972
Stonefly, Pteronarcys californica	S	U	Lindane	96	4.5	4	Sanders & Cope, 1968
Midge, Chironomus tentans	S	U	Lindane	48	207	175	Macek, et al. 1976

* S = static

** U = unmeasured, M = measured

Geometric mean of adjusted values for lindane = 62 µg/l $\frac{62}{21}$ = 2.9 µg/l

Table 3. Freshwater fish chronic values for hexachlorocyclohexane* (Macek, et al. 1976)

Organism	Test**	Limits (ug/l)	Chronic Value (ug/l)***
Fathead minnow, Pimephales promelas	LC	9.1-23.5	14.6

* Data for lindane

** LC = life cycle or partial life cycle

*** Measured

Geometric mean of chronic values = 14.6 µg/l $\frac{14.6}{6.7}$ = 2.2 µg/l

Lowest chronic value = 14.6 µg/l

Table 4. Freshwater invertebrate chronic values for hexachlorocyclohexane* (Macek, et al. 1976)

Organism	Test**	Limits (ug/l)	Chronic Value (ug/l)***
Cladoceran, *Daphnia magna*	LC	11-19	14.5
Scud, *Gammarus fasciatus*	LC	4.3-8.6	6.1
Midge, *Chironomus tentans*	LC	2.2-5.0	3.3

* Data for lindane

** LC = life cycle or partial life cycle

*** All values measured

Geometric mean of chronic values = 6.6 µg/l $\quad \frac{6.6}{5.1} = 1.3$ µg/l

Lowest chronic value = 3.3 µg/l

Table 5. Freshwater plant effects for hexachlorocyclohexane* (Krishnakumari, 1977)

Organism	Effect	Concentration (ug/l)
Alga, Scenedesmus acutus	>20% growth inhibition in 5 days	1,000 (BHC tech)
Alga, Scenedesmus acutus	>20% growth inhibition in 5 days	500 (alpha BHC)
Alga, Scenedesmus acutus	>20% growth inhibition in 5 days	5,000 (beta BHC)
Alga, Scenedesmus acutus	>20% growth inhibition in 5 days	1,000 (gamma BHC)

* Tested isomer listed

Lowest plant value = Lindane = 1,000 µg/l

BHC = 1,000 µg/l

Table 6. Freshwater residues for hexachlorocyclohexane

Organism	Bioconcentration Factor	Time (days)	Reference
Zooplankton,	336*	5-60	Hamelink & Waybrant, 1976
Rainbow trout, Salmo gairdneri	486*	108	Hamelink & Waybrant, 1976
Brook trout, Salvelinus fontinalis	70* ***	261	Macek, et al. 1976
Fathead minnow, Pimephales promelas	477* ***	304	Macek, et al. 1976
Bluegill, Lepomis macrochirus	35* ***	735	Macek, et al. 1976
Bluegill, Lepomis macrochirus	340*	5-81	Hamelink & Waybrant, 1976

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Domestic animals	Animal feed	0.1*	U.S. FDA Admin. - Guideline 7426.04
Domestic animals	Animal feed	0.1**	U.S. FDA Admin. - Guideline 7426.04
Man	Frog legs	0.5**	U.S. FDA Admin. - Guideline 7420.08

* Lindane

** BHC

***Muscle tissue for bluegill and brook trout and eviscerated fathead minnows.
Geometric mean whole body fish bioconcentration factor for lindane = 406
Lowest permissible residue concentration for lindane = 0.1 mg/kg
Highest geometric mean whole body bioconcentration factor for a single species for lindane = 486

$\frac{0.1}{486}$ = 0.00021 mg/kg or 0.21 µg/l

Table 7. Other freshwater data for hexachlorocyclohexane

Organism	Test Duration	Effect	Result (ug/l)	Reference
		Lindane		
Rainbow trout, Salmo gairdneri	6 wks	Lethal threshold concentration	22	Tooby & Durbin, 1975
Brook trout, Salvelinus fontinalis	11 days	LC50	26	Macek, et al. 1976
Brook trout, Salvelinus fontinalis	261 days	Reduced growth	16.6	Macek, et al. 1976
Fathead minnow, Pimephales promelas	11 days	LC50	62	Macek, et al. 1976
Fathead minnow, Pimephales promelas	11 days	LC50	76	Macek, et al. 1976
Bluegill, Lepomis macrochirus	21 days	LC50	29	Macek, et al. 1976
Bluegill, Lepomis macrochirus	21 days	LC50	31	Macek, et al. 1976
Chorus frog (tadpole), Pseudacris triseriata	96 hrs	LC50	2,700	Sanders, 1970
Toad (tadpole), Bufo woodhousii	96 hr	LC50	4,400	Sanders. 1970
		BHC		
Tubifex and Limnodrilus mixture	96 hrs	LC50	3,150	Whitten & Goodnight, 1966
Chinook salmon, Oncorhynchus tshawytscha	10 hrs	LC100	100	Anonymous, 1960
Rainbow trout, Salmo gairdneri	44½ hrs	LC100	100	Anonymous, 1960
Toad (tadpole), Bufo woodhousii	96 hrs	LC50	3,200	Sanders, 1970

Table 7. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
		Alpha Hexachlorocyclohexane		
Pond snail, Lymnaea stagnalis	40 days	EC50 egg production inhibition	250	Canton & Slooff, 1977
Pond snail, Lymnaea stagnalis	40 days	EC50 embryonic development		Canton & Slooff, 1977
Pond snail, Lymnaea stagnalis	40 days	Reproductive inhibition	65	Canton & Slooff, 1977
Cladoceran Daphnia magna	25 days	EC50 reproduction	100	Canton, et al. 1975

SALTWATER ORGANSMS

Introduction

Hexachlorocyclohexane is an insecticide, primarily consisting of five configurational isomers, sold under the trade names, BHC (benzene hexachloride) and Compound-666. Technical grade BHC contains isomers in the following ranges: alpha-isomer, 55 to 70 percent; beta-isomer, 6 to 8 percent; gamma-isomer, 10 to 18 percent; delta-isomer, 3 to 4 percent; and epsilon isomer, trace amounts. Since the gamma-isomer (lindane, a pesticide) is the isomer with insecticidal properties and is most toxic to aquatic organisms, lindane is the most important hexachlorocyclohexane isomer for which to establish a water quality criterion.

The data base for the toxicity of BHC or lindane to saltwater organisms includes acute toxicity tests on 13 fish and 8 invertebrate species (Tables 8, 9, and 12), toxicity tests on algae (Table 10), and bioconcentration tests with oysters, shrimp and fish (Table 11 and 12). No data are available on the chronic toxicity of hexachlorocyclohexane to any fish or invertebrate species.

Acute Toxicity

Saltwater fishes have a wide range of sensitivity to lindane. Thirteen species of fishes were tested in static and flow-through exposures. Only two species were tested for 96 hours under flow-through conditions with measured concentrations. The LC50 values for the pinfish were 30.6 µg/l and for sheepshead minnow, 103.9 µg/l (Schimmel, et al. 1977). The LC50 values for the 11 other species, after adjusting for test conditions, have a range from

4.9 to 149.7 µg/l (Butler, 1963; Eisler, 1970; Katz, 1961; Korn and Earnest, 1974) indicating considerable variation in species sensitivity.

Only one test was conducted on a saltwater fish using BHC. The 96-hour flow-through LC50 with measured concentrations was 86.4 µg/l for pinfish (Schimmel, et al. 1977). This compares to a 30.6 µg/l LC50 for the same species under the same conditions for lindane indicating a lesser toxicity for BHC (Schimmel, et al. 1977). Adjusted LC50 values for 16 freshwater fishes exposed to lindane, 1 to 83 µg/l (Table 1), were similar to those of saltwater fishes.

When the geometric mean of the adjusted LC50 values for lindane is divided by the species sensitivity factor (3.7), a value of 6.2 µg/l is obtained. Since this value is close to, but less than, several of the lowest adjusted LC50 values in Table 8, the species sensitivity factor seems reasonable. The Final Fish Acute Value is 6.2 µg/l, a value expected to be equal to or less than the LC50 value for 95 percent of all saltwater fish species.

The 96-hour LC50 value of BHC to pinfish is the only acute value, and when it is adjusted for species sensitivity, the Final Fish Acute Value is 23 µg/l.

Invertebrate LC50 or EC50 values for BHC and lindane range from 0.13 to 346 µg/l, after adjusting for test conditions (Table 9). With the exception of the American oyster, invertebrate species are generally more sensitive than are saltwater fishes to lindane. The commercially important pink shrimp and brown shrimp are more than one order of magnitude more sensitive than the

second most sensitive species. The American oyster has an adjusted 96-hour EC50 value of 346.5 µg/l based on decreased shell deposition (Butler, 1963). This value is over 2,000 times greater than the value for the most sensitive species, indicating a much greater tolerance than the other species tested and the need for a larger species sensitivity factor for invertebrate species than for fishes. Adjusted LC50 values for 8 freshwater invertebrate species exposed to lindane ranged from 4 to 745 µg/l (Table 2), indicating that they may be slightly less sensitive than saltwater species.

A single invertebrate LC50 was available for BHC. The LC50 value for pink shrimp of 0.34 µg/l indicates that BHC is less toxic than lindane (Schimmel, et al. 1977).

The geometric mean of the adjusted LC50 values for lindane divided by the species sensitivity factor (49) gives a Final Invertebrate Acute Value of 0.076 µg/l, which is about one-half the lowest value. Since there are data for only 7 species, the calculated Final Invertebrate Acute Value of 0.076 µg/l appears reasonable and becomes the Final Acute Value for lindane.

The 96-hour LC50 of BHC for the only species tested, pink shrimp, was 0.34 µg/l. Since this species is exceptionally more sensitive to lindane than the other invertebrate species, it would be unreasonable to divide the single LC50 for the pink shrimp and BHC by the sensitivity factor. Thus the Final Invertebrate Acute Value for BHC would be 0.34 µg/l.

Plant Effects

Only three published studies were found on the effect of hexachlorocyclohexane on plants (Table 10). The first was concerned with the effects of lindane on the marine alga, Acetabularia mediterranea (Borghi, et al. 1973). Concentrations of 10,000 µg/l inhibited cell growth and morphogenesis following at least 3 days exposure. Exposures of 2 days or less showed no effect on the alga. The growth inhibition that occurred was reversible when the alga was removed from lindane. The growth inhibition was apparently related to the fact that the alga appeared to become dormant during exposure.

The second study (Canton, et al. 1977) reported that alpha-hexachlorocyclohexane showed no toxicity to the marine alga Chlamydomonas sp., at concentrations up to the solubility limit for the culture medium.

The third study (Butler, 1963) observed a 28.5 percent decrease in productivity of natural phytoplankton communities at a concentration of 1,000 µg lindane/l.

Residues

The bioconcentration of hexachlorocyclohexane from water into the tissues of saltwater organisms has been relatively well studied (Table 11). Probable steady-state bioconcentration factors (BCF's) are available for American oysters and pinfish (Schimmel, et al. 1977). Additional BCF data (Table 12) probably are not at steady-state from two-hour exposures of two species of algae (Canton, et al. 1977) and from 4-day exposures of grass shrimp, pink shrimp, sheepshead minnow, and pinfish (Schimmel et al. 1977).

Compared to many of the chlorinated insecticides, the bioconcentration factors at steady-state are low. American oysters exposed continuously for 28 days to BHC bioconcentrated an average of 218 times the amount measured in the exposure water. Only in the highest exposure concentration, 0.093 µg/l, did the insecticide accumulate sufficiently high for accurate measurement. Pinfish exposed to BHC for 28 days bioconcentrated in edible tissue an average of 130 times the amount in water. The average BCF in offal (head and viscera) was 617. The relative percentages of the four isomers in BHC were similar to those in pinfish offal and edible tissues. Apparently, no individual isomer was stored or purged selectively. Oysters and pinfish depurated all detectable BHC within one week after being placed in BHC-free water. The Residue Limited Toxicant Concentration is 0.27 µg/l based on an average fish BCF of 374 and a FDA limit of 0.1 mg/kg for animal feed.

Additional data on the bioconcentration of BHC and lindane are available for other organisms, but it is doubtful that the concentrations in the organisms, are at steady-state. The average bioconcentration factors after 4 days of exposure to lindane were 63 for grass shrimp, 84 for pink shrimp, 450 for sheepshead minnow, and 218 for pinfish (Schimmel, et al. 1977). In the same study, the average bioconcentration factors after 4 days of exposure to BHC were 80 for pink shrimp and 482 for pinfish. The four isomers of BHC were bioconcentrated in tissues of pink shrimp and pinfish in approximately the same relative amounts as in the insecticide formulation. Saltwater phytoplankters rapidly accumulate and depurate BHC (Canton, et al. 1977).

Miscellaneous

Other data included in the tables but not yet discussed do not contribute significantly to the derivation of a criterion for BHC or lindane.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

Lindane

Final Fish Acute Value = 6.2 µg/l

Final Invertebrate Acute Value = 0.076 µg/l

Final Acute Value = 0.076 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 1,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1,000 µg/l

0.44 x Final Acute Value = 0.033 µg/l

BHC

Final Fish Acute Value = 23 µg/l

Final Invertebrate Acute Value = 0.34 µg/l

Final Acute Value = 0.34 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = 0.27 µg/l

Final Chronic Value = 0.27 µg/l

0.44 x Final Acute Value = 0.15 µg/l

Lindane

No saltwater criterion can be derived for lindane using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

BHC

No saltwater criterion can be derived for a mixture of isomers of BHC using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 8. Marine fish acute values for hexachlorocyclohexane

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, Anguilla rostrata	S	U	***	96	56.0	30.6	Eisler, 1970
Sheepshead minnow, Cyprinodon variegatus	FT	M	****	96	103.9	103.9	Schimmel, et al. 1977
Mummichog, Fundulus heteroclitus	S	U	***	96	60.0	32.8	Eisler, 1970
Striped killifish, Fundulus majalis	S	U	***	96	28.0	15.3	Eisler, 1970
Longnose killifish, Fundulus similis	FT	U	****	48	240.	149.7	Butler, 1963
Atlantic silverside, Menidia menidia	S	U	***	96	9.0	4.9	Eisler, 1970
Threespine stickleback, Gasterosteus aculeatus	S	U	****	96	44.0	24.1	Katz, 1961
Threespine stickleback, Gasterosteus aculeatus	S	U	****	96	50.0	27.3	Katz, 1961
Striped bass, Morone saxatilis	FT	U	****	96	7.3	5.6	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT	M	*****	96	86.4	86.4	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	FT	M	****	96	30.6	30.6	Schimmel, et al. 1977
Bluehead, Thalassoma bifasciatum	S	U	***	96	14.0	7.7	Eisler, 1970
White mullet, Mugil curema	FT	U	****	48	30.0	18.7	Butler, 1963
Striped mullet, Mugil cephalus	S	U	***	96	66.0	36.1	Eisler, 1970

Table 8. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Northern puffer, Sphaeroides maculatus	S	U	***	96	35.0	19.1	Eisler, 1970

* S = static; FT = flow-through

** M = measured; U = unmeasured

*** Entomol. Soc. Am. Reference Standard for Lindane

**** Technical grade Lindane

*****BHC (21% α-BHC, 39% γ-BHC, 2.1% β-BHC, 23% Δ-BHC, 14.9% unidentified compounds)

Geometric mean of adjusted values: lindane = 23.0 µg/l $\frac{23.0}{3.7}$ = 6.2 µg/l

BHC = 86.4 µg/l $\frac{86.4}{3.7}$ = 23 µg/l

Lowest value from a flow-through test with measured concentrations: lindane = 30.6 µg/l

BHC = 86.4 µg/l

Table 9. Marine invertebrate acute values for hexachlorocyclohexane

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American oyster, Crassostrea virginica	FT	U	***	96	450******	346.5	Butler, 1963
Mysid, Mysidopsis bahia	FT	M	***	96	6.28	6.28	Schimmel, et al. 1977
Sand shrimp, Crangon septemspinosa	S	U	****	96	5.0	4.2	Eisler, 1969
Hermit crab, Pagurus longicarpus	S	U	****	96	5.0	4.2	Eisler, 1969
Grass shrimp, Palaemonetes pugio	FT	M	***	96	4.44	4.44	Schimmel, et al. 1977
Grass shrimp, Palaemonetes vulgaris	S	U	****	96	10.0	8.5	Eisler, 1969
Brown shrimp, Penaeus aztecus	FT	U	***	48	0.4******	0.13	Butler, 1963
Pink shrimp, Penaeus duorarum	FT	M	***	96	0.17	0.17	Schimmel, et al. 1977
Pink shrimp, Penaeus duorarum	FT	M	*****	96	0.34	0.34	Schimmel, et al. 1977

* S = static; FT = flow-through
** M = measured; U = unmeasured
*** Technical grade lindane (100% γ-BHC)
**** Entomol. Soc. Am. Reference Standard for Lindane
***** BHC (21% α-BHC, 39% γ-BHC, 2.1% β-BHC, 23% Δ-BHC, 14.9% unidentified compounds)
******EC50: decreased shell growth in oysters or loss of equilibrium in pink shrimp.

Geometric mean of adjusted values: lindane = 3.7 µg/l $\frac{3.7}{49}$ = 0.076 µg/l

BHC = 0.34 µg/l $\frac{0.34}{49}$ = 0.0069 µg/l

Lowest value from a flow-through test with measured concentrations: lindane = 0.17 µg/l
BHC = 0.34 µg/l

Table 10. Marine plant effects for hexachlorocyclohexane

Organism	Effect	Concentration (ug/l)	Reference
Natural phytoplankton communities	28.5% decrease in productivity, ^{14}C.	1,000*	Butler, 1963
Alga, *Acetabularia mediterranea*	Inhibition of cell growth and cell morphogenesis, reversible.	10,000*	Borghi, et al. 1973
Alga, *Chlamydomonas* sp.	No effect in short term toxicity (48 hr)	Solubility limit**	Canton, et al. 1977

* Lindane

**α-BHC

Lowest plant value for lindane = 1,000 µg/l

Table 11. Marine residues for hexachlorocyclohexane (Schimmel, et al. 1977)

Organism	Bioconcentration Factor	Time (days)
American oyster, Crassostrea virginica	218*	28
Pinfish, Lagodon rhomboides	130*, **	28
Pinfish, Lagodon rhomboides	617*, ***	28

Maximum Permissible Tissue Concentration

Organsim	Action Level or Effect	Concentration (mg/kg)	Reference
Domestic animals	Animal feed	0.1****	U.S. FDA Admin., Guideline 7426.04
Man	Frog legs (meat only)	0.5*****	U.S. FDA Admin., Guideline 7420.08
Domestic animals	Animal feed	0.1*****	U.S. FDA Admin., Guideline 7426.04

* Technical grade BHC (21% α-BHC, 39% γ-BHC, 2.1% β-BHC, 23% Δ-BHC, 14.9% unidentified compounds)

** Edible tissue

*** Offal tissue

**** Lindane

***** BHC

Average fish bioconcentration factor for BHC = 374.

Lowest residue concentration for BHC = 0.1 mg/kg

$\frac{0.1}{374}$ = 0.00027 mg/kg or 0.27 μg/l

Table 12. Other marine data for hexachlorocyclohexane

Organism	Test Duration	Effect	Result (µg/l)	Reference
Alga, Chlamydomonas	2 hrs	f*310	10**	Canton, et al. 1977
Alga, Chlamydomonas	2 hrs	f*2700	1,000**	Canton, et al. 1977
Alga, Dunaliella	2 hrs	f*1500	1,000**	Canton, et al. 1977
Grass shrimp, Palaemonetes pugio	4 days	Bioconcentration factor = 63	***	Schimmel, et al. 1977
Brown shrimp, Penaeus aztecus	24 hrs	LC50	35****	Chin & Allen, 1957
Pink shrimp, Penaeus duorarum	4 days	Bioconcentration factor = 84	***	Schimmel, et al. 1977
Pink shrimp, Penaeus duorarum	4 days	Bioconcentration factor = 80	*****	Schimmel, et al. 1977
White and brown shrimp, Penaeus setiferus Penaeus aztecus	24 hrs	LC50	400****	Chin & Allen, 1957
Sheepshead minnow, Cyprinodon variegatus	4 days	Bioconcentration factor = 490	***	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	4 days	Bioconcentration factor = 218	***	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	4 days	Bioconcentration factor = 482	*****	Schimmel, et al. 1977

* f-Freundlich isotherm (concentration (α-BHC) in algae (µg/g)/Concentration (α-BHC) in water phase (µg/ml)

** α-Hexachlorocyclohexane (α-BHC)

*** Technical grade lindane

**** Tri-6 Dust No. 30 (3.0% γ-BHC, 5.1% other isomers BHC, 91.9% inert). Result based on µg/l Tri-6 Dust No. 30.

***** Technical grade BHC (21% α-BHC, 39% γ-BHC, 2.1% β-BHC, 23% Δ-BHC, 14.9% unidentified compounds)

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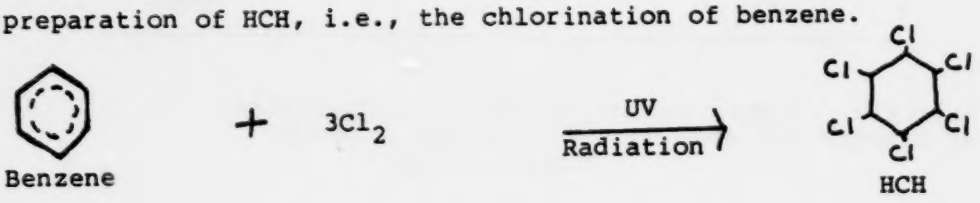
Mammalian Toxicology and Human Health Effects

Introduction

Hexachlorocyclohexane (HCH) was first synthesized in 1825 by Faraday. The insecticidal properties of HCH were demonstrated by the American chemist Bender in 1933 and later by the French chemist Dupire in 1940. One of the common names for HCH is BHC (benzene hexachloride). This is obviously a misnomer since HCH is a saturated chlorinated hydrocarbon and, therefore, has no aromaticity. The common "misname", BHC, probably came from the original method of preparation of HCH, i.e., the chlorination of benzene.



This preparation method yields technical grade HCH which is a mixture of the five basic isomers (see Figure 1). The composition of technical HCH is approximately as follows:

Isomer	Percent
alpha (α)	60-70
beta (β)	5-12
gamma (γ)	10-15
delta (δ)	6-10
epsilon (ϵ)	3-4

The gamma isomer (γ -HCH) has the lowest melting point (112.8°C) and the highest acute toxicity and is commonly called lindane.

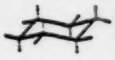
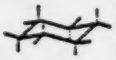
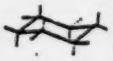
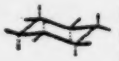
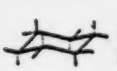
Isomer	% in techn. BHC	Melting point	Vapour pressure mmHg 20 • C	Polarity	Refraction index nD 20	Wave length in angström	Configuration Cl — H	Crystal
α	60-70	157,5-158,5	0,02	2,22:	1,60 -1,626	1258		monoclinic prisms
β	5-12	309	0,005	0	1,630	1346		cubic (octahedral)
γ	10-15	112,8	0,03	2,8: 3,6	1,60 -1,635	1322		monoclinic crystals
δ	6-10	138-139	0,02	2,2: (2,17: 2,32)	1,576-1,674	1181		crystals or fine platelets
ε	3- 4	218,8		0	1,00 -1,635	1396		monoclinic needles or hexagonal monoclinic crystals
ζ		68 - 88						
η		89,8- 90,5						
θ		124 -125						

Figure 1. Comparison of the Physical Constants of Lindane and some of the other BHC Isomers (Ulmann, 1972)

Lindane, named after the Belgian chemist, van der Linden, has been marketed under a number of trade names as an insecticide including the following registered trademarks:

Jacutin	(emulsifiable concentrate)
Lindafor 90	(wettable powder)
Lindamul 20	(emulsifiable concentrate)
Nexit-Staub	(0.8 percent dust)
Prodactic	(wettable powder)

Other names for γ-HCH include γ-BHC, γ-lindane, purified BHC, and technical lindane. The common names in Sweden, Denmark, and the USSR are hexaklor, 666, and hexachloran, respectively. It is important to recognize the various synonyms for HCH and its isomers due to the extensive use and misuse of these names in the literature. In this document, HCH will be used as an abbreviation for hexachlorocyclo-

hexane and its synonyms. However, the various isomers will be designated by the appropriate Greek letter. Lindane will be referred to as γ-HCH. The technical product will be t-HCH.

The major commercial usage of HCH is based upon its insecticidal properties. As indicated previously, the -γ isomer has the highest acute toxicity, but the other isomers are not without activity. It is generally advantageous to purify the γ-isomer from the less active isomers. The γ-isomer acts on the nervous system of insects, principally at the level of the nerve ganglia (Block and Newland, 1974). As a result, lindane has been used against insects in a wide range of applications including treatment of animals, buildings, man for ectoparasites, clothes, water for mosquitoes, living plants, seeds and soils. Some applications have been abandoned due to excessive residues, e.g., stored foodstuffs.

EXPOSURE

Ingestion from Water

The contamination of water with HCH has occurred principally from two sources:

(1) direct application of γ-HCH or technical HCH to aquatic systems for the control of mosquitoes

(2) the use of HCH in agriculture and forestry.

The contamination of water supplies from agriculture and forestry comes usually from HCH associated with soil or sediment particles (Lotse, et al. 1968). The only other major source of aquatic pollution of HCH occasionally occurs during its manufacture. HCH-containing waste water can be generated during the synthesis, crystallization, and isomer separation. These HCH contaminated waste waters are usually cleaned up prior to discharge, but occasionally some contamination occurs.

The occurrence of HCH in water supplies is potentially more of a problem than for many other organochlorine insecticides, such as DDT, endrin, aldrin, heptachlor, etc., due to HCH's high water solubility. Solubility of γ-HCH is 7.3 ppm at 25°C, 12 ppm at 35°C and 14 ppm at 45°C (Gunther, et al. 1968). However, the different HCH isomers exhibit different solubilities at a constant temperature, e.g.,

	Sol. @ 30°C	Vapor Pressure (Natl. Acad. Sci., 1975)
alpha	10 ppm	0.06 torr
beta	5 ppm	0.17 torr
gamma	10 ppm	0.14 torr

γ-HCH has been detected in the finished water of Streator, Illinois at 4 μg/liter (U.S. EPA, 1975). γ-HCH has a low residence time in the aquatic environment and the principal routes by which γ-HCH disappears are sedimentation, metabo-

lism, and volatilization. γ-HCH is generally found to contribute less to aquatic pollution than the other HCH isomers (Henderson, et al. 1971).

Ingestion from Foods

Duggan and Duggan (1973) tabulated the human daily intake for γ-HCH and other HCH isomers. For γ-HCH the daily intake was 1 to 5 µg/kg body weight/day and was 1 to 3 µg/kg/day for all other isomers of HCH. Assuming a 70-year lifespan for a 70 kg man, his lifetime ingestion would be 1.8 to 8.9 grams of γ-HCH, and 1.8 to 5.4 grams of all other isomers of HCH. Engst, et al. (1976) in a study of German citizens, determined that a male of 65 kg would consume 0.25 mg of γ-HCH in 70 years. Reasons for the large difference in the two investigations are apparently due to exposure and consumption of fish products.

The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products. Seafood as a source of HCH for humans is usually minor, which may be attributed to the relatively high rate of dissipation of HCH in the aquatic environment. γ-HCH and other HCH isomer residues have generally been of low order of magnitude.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent

lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 340 was obtained for lindane using bluegills containing about one percent lipids (Hamelink and Waybrant, 1976). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for lindane and the edible portion of all aquatic organisms consumed by Americans is calculated to be 340 x 2.3 = 780.

Inhalation

Little is known about the concentration and distribution of γ-HCH in the atmosphere. Abbott, et al. (1966) found only traces of HCH in air in central and suburban London. According to an investigation by Barney (1969) the γ-HCH intake by inhalation is 0.002 µg/kg/day, while the FAO/WHO A.D.I. limit is 1 µg/kg/day (Natl. Acad. Sci., 1977). Hesse, et al. (1976) showed that short term inhalation of HCH by men did not lead to a significant increase of the compound in the blood and urine and had no influence on serum enzymes either immediately or within 21 to 24 days after exposure. Voitenko (1978) described a synergistic action for γ-HCH administered through both the gastrointestinal (1.5 mg/kg/day) and respi-ratory (0.84 mg/m^3) tracts for four months in albino rats.

Dermal

γ-HCH has been used in human and veterinary dermatology against ectoparasites for more than 25 years. Many publications express good dermal tolerance and there is little mention of adverse skin reaction. In a few cases, dermal reactions after contact with γ-HCH preparations have been described as local irritation and an occasional case of eczema has been described. The adverse experiences with man have usually been with concentrated liquid formulations. All these reactions healed after scab formation.

PHARMACOKINETICS

Absorption

The rapidity of γ-HCH absorption is enhanced by lipid mediated carriers. For an organochlorine insecticide, lindane is unusually soluble in water, another factor contributing

to its rapid absorption and excretion (Herbst and Bodenstein, 1972).

Fisher 344 rats were treated with daily oral injections of peanut oil spiked with γ-HCH which was ^{14}C labeled. For 2 mg administered orally, only 0.1 to 4 μg γ-HCH was found in the urine, representing 0.005 to 0.2 percent of intact γ-HCH. However, 2 to 5 percent of the original γ-HCH was found in the feces (Chadwick, 1971; Chadwick, 1979). It can be concluded from these data that γ-HCH is not generally excreted in the urine but is in the feces. Excretion from the feces comprises only a small percentage of the original orally administered dose.

An oil solution containing 40 mg γ-HCH per kg body weight was injected intraperitonally to rats, resulting in 35 percent absorption. At the end of a 24 hour period, 10 percent of the original amount still remained in the abdominal cavity (Koransky, et al. 1963). Low lindane levels in the intestinal wall indicated a very rapid absorption process.

Ginsburg, et al. (1977) studied the dermal absorption of lindane in infants and children. Twelve children with infection caused by Sarcoptes scabiei and eight non-infected siblings for whom prophylactic γ-HCH had been prescribed were included in the investigation. Blood specimens were obtained at 2, 4, 6, 8, 12, 24, and 48 hours after the topical application of one percent γ-HCH lotion. γ-HCH was detected in the blood at all times, with peak concentration noticed six hours after application. An absorption half-life of 17.9 hours in the blood of infected children was recorded

and 210.4 hours in children with normal skin. These findings support previous observations in animals and adult human volunteers that lindane is absorbed through the skin.

Distribution

γ-HCH has reached detectable levels in the brain, liver, skin, and musculature of mice in as little as three hours after administration (van Asperen, 1958). Carbon-14 tagged γ-HCH administered to rats intraperitoneally in a dose of 14 mg/kg body weight was noticed very quickly in the fatty tissues. At least 75 percent of the labeled γ-HCH was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Another experiment utilizing ^{14}C labeled HCH isomers revealed a uniform distribution in adipose tissue throughout the body of mice (Nakajima, et al. 1970). On the other hand, concentration of γ-HCH in the brain at a level higher than other organs is supported in the literature (Laug, 1948; Davidou and Frawley, 1951; Koransky, et al. 1963; Huntingdon, 1971).

A 17 mg/kg body weight dose of lindane in rape oil given orally to calves showed a 0.62 ppm blood level after three hours, 2.0 ppm after 24 hours and 0.124 ppm after seven days. Only barely detectable levels were found at three and six weeks subsequent to application (Kadis and Jonasson, 1965).

γ-HCH has also been noted to enter the fetus through the placenta. Residue levels of various pesticides, including lindane, were found in the fatty tissue of pregnant women and in the vernix careosa of their newborn babies. In some women with a normal course of pregnancy, pesticide

concentrations were extraordinarily high, but did not cause premature termination of the pregnancy or noticeably affect intrauterine fetal development (Poradovsky, et al. 1977). Analysis of macroscopically normal appearing human embryos and fetuses obtained from abortion cases revealed detectable levels of β-HCH (Nishimura, et al. 1977). Higher concentrations were found in the skin than in the brain. Levels in the skin of more highly developed fetuses were greater as a result of a more highly developed skin fat content. Concentration never exceeded the corresponding values of normal adult organs.

In an accidental case of human poisoning, 0.29 ppm γ-HCH was found in the blood plasma during the convulsive phase, and decreased to a 0.02 ppm level seven days later (Dale, et al. 1966). Several authors have reported on the level of α-HCH in human milk (Savage, et al. 1973; Curley and Kimbrough, 1968). Bakken and Siep (1977) found that approximately 56 percent of those persons examined in Norway showed milk levels of HCH greater than the maximum approved concentration for cows' milk by the World Health Organization.

Metabolism

The biological transformation of hexachlorocyclohexane isomers in mammals results in the formation of various chlorophenols including: 2,4,5, and 2,3,5-trichlorophenol; 2,3,4,5-tetrachlorophenol; 2,4,6-trichlorophenol; 3,4,-dichlorophenol; 2,3,4,6-tetrachlorophenol; 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol (PCCOL); and 3,4-dichlorophenylmercapturic acid. These are commonly excreted in the urine as conjugates of sulfuric and glucuronic acid, (Grover and Sims, 1965; Freal

and Chadwick, 1973; Chadwick and Freal, 1972). These metabolites have been found in the blood, liver, kidneys, spleen, heart, and brain of rats fed γ-HCH, but were not detected in the intestine or feces (Engst, et al. 1976). Freal and Chadwick (1973) originally suggested γ-HCH is metabolized in the rat to a series of metabolites ranging from pentachlorocyclohexenes to trichlorobenzenes and resulting in chlorophenols. Chadwick, et al. (1975) later demonstrated that γ-HCH undergoes metabolism to an intermediate hexachlorocyclohexene, from which further degradation yields PCCOL, two tetrachlorophenols and three trichlorophenols. This metabolic pathway was not observed for the other hexachlorocyclohexane isomers. Freal and Chadwick (1973) also noted an enhanced metabolism of γ-HCH upon pretreatment with the other BHC isomers. This enhancement decreased in the order of alpha-delta-gamma-beta. DDT, mirex, chlordane, and HCB also stimulate the metabolism of γ-HCH significantly (Chadwick, et al. 1977a). The preapplication of γ-HCH has also been shown to stimulate its own biodegradation in rats (Noack, et al. 1975).

Pretreatment of male Wistar rats with cadmium also has been noted to alter γ-HCH metabolism. Three days after exposure to ^{14}C γ-HCH, the control rats excreted significantly more radioactivity than the Cd-treated groups. Cd-exposure altered the distribution of neutral and polar γ-HCH metabolites, as well as inhibiting the dehydrogenation of γ-HCH to hexachlorocyclohexene (Chadwick, et al. 1978).

The administration of dimethyl sulfoxide with γ-HCH to female rats led to impaired γ-HCH metabolism and lowered

specific microsomal phospholipid content indicated some interaction between γ-HCH, dimethyl sulfoxide, and dietary lipids (Chadwick, et al. 1977b).

Dietary fibers are known to have protective effects against a variety of chemical toxicants through metabolic alterations. Chadwick, et al. (1977c) demonstrated that rats fed diets supplemented with fiber showed a higher dehydrogenation and dechlorination of γ-HCH and suggests a substantial alteration in the excretion and metabolism of γ-HCH and its metabolites in mammals.

Trichlorophenols also result from the metabolism of isomers other than γ-HCH, although it seems that tetrachlorophenols are not produced. The excretion of mercapturic acid conjugates has also been noted (Kurihara, 1977). Using rat liver preparation, Portig, et al. (1973) detected the direct glutathione dependent conversion of α-HCH. Eliminated products of HCH metabolism, both free and conjugated chlorophenols, are far less toxic, however, than the parent compounds (Natl. Acad. Sci., 1977). A recent proposed degradation scheme is shown in Figure 2 (Chadwick, 1978, in press).

Excretion

Continual administration of γ-HCH to an organism will lead to an equilibrium concentration and stabilization. This equilibrium concentration occurs as continuing intake is offset by degradation and elimination of the γ-HCH.

Kitamura, et al. (1970) has investigated the rate of elimination of γ-HCH as compared to β-HCH. Figure 3 shows that β-HCH is excreted at a much slower rate. Since the pure β-isomer seems to persist in the body, there is justifi-

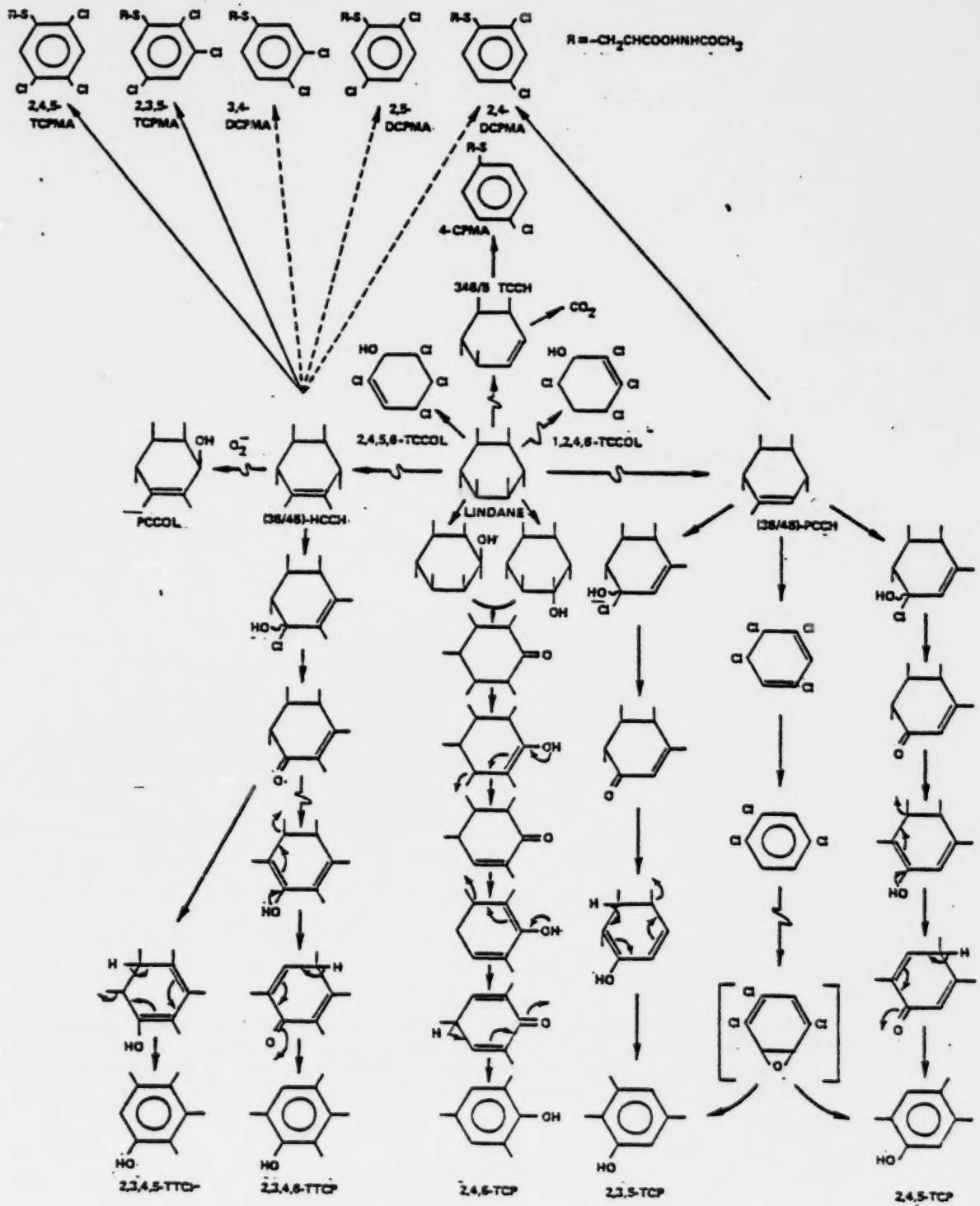


Figure 2. Metabolism of Lindane.

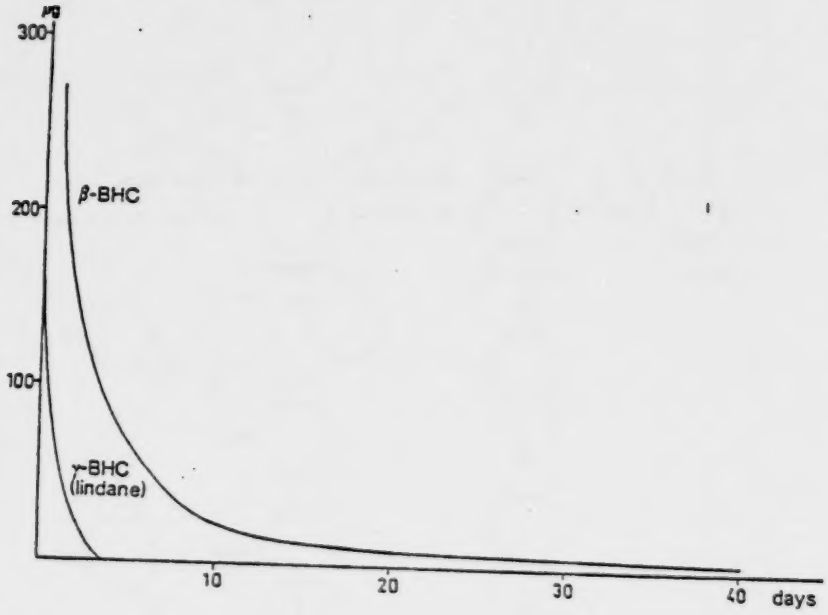


Figure 3. Reduction of HCH concentration in the total mouse body, excluding the skin and the digestive tract, after a single oral dose of 500 mcg γ-HCH and 500 mcg β-HCH (Kitamura, et al. 1970)

cation for the use of only the pure form of the γ-isomer in situations that might lead to absorption. The rapid biological deterioration of γ-HCH is self-induced and minimizes the health hazards presented by hexachlorocyclohexanes (Sieper, 1972; Chadwick, et al. 1971; Chadwick and Freal, 1972).

Even prolonged γ-HCH administration results in complete elimination when application has been terminated. In one experiment a γ-HCH concentration in rat fatty tissues of 102 ppm was achieved. One week subsequent to cessation of administration, the concentration had dropped to zero. Similar results were obtained when it was found that 281 ppm fatty tissue was eliminated within two weeks (Frawley and Fitzhugh, 1949; Lehman, 1952). After rats were fed 100 ppm of γ-HCH over a ten day period, it was found that three days following discontinuation of treatment quantities in the body had diminished to 0.1 ppm. Similarly, 24 hours after cessation of feeding rats 10 ppm γ-HCH for 20 days, no residue could be detected using gas chromatography with an electron capture detector (Kitamura, et al. 1970).

Only very slight amounts of unaltered γ-HCH are excreted. Dietary intake by rats for one month revealed only about four percent in the urine at the end of feeding period (Laug, 1948). No excretory traces of unchanged lindane have been noticed with intraperitoneal injections. The main excretory products in urine are water soluble conjugates of glucuronide, mercapturic acid, conjugates, and sulfate. Single oral administrations to rats of 50 to 100 mg lindane per kg body weight resulted in 1.5 mg per day increase of urinary glu-

curonic acid excretion within about two weeks. Organic sulfur compound excretion was enhanced by about 35 to 58 percent (Rusiecki and Bronisz, 1964). When given at 20 mg/kg body weight, an increase in glucuronic acid excretion was noticed after two days (Chadwick, et al. 1971; Chadwick and Freal, 1972).

HCH is eliminated not only by urinary excretion, but also via milk secretions. It commonly exists in low concentrations in human milk. Usually the β-isomer accounts for 90 percent of the HCH present. The α and γ isomers account for the remaining 10 percent (Herbst and Bodenstein, 1972).

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Of the various isomers of HCH, γ exhibits the greatest acute toxicity to mammalian organisms. This toxicity varies with the species subject. Toxicity also varies with route of administration which in turn controls absorption. Intravenous administration produces the most severe injury, followed by intraperitoneal, subcutaneous, oral and dermal exposure (Shirakowa, 1958). As a general rule, formulations of HCH in oil and fat induce a higher toxicity than most, while the least toxic form is the pure crystalline chemical. Toxicity variations are also noted among different types of oils or solvents (Starek and Zabinski, 1970).

It has been demonstrated that young animals are more sensitive to the toxic effects of γ-HCH than adults of the same species (Shirakowa, 1959; Radaleff and Bushland, 1960). The increased sensitivity of young mammals to intoxication, at least to the age of weaning, is a result of low

production of liver enzymes affecting detoxification at an early age (Fouts and Adamson, 1959). Diseased and distressed animals show a similar pattern (Chen, 1968).

γ-HCH has a higher acute toxicity than many other chlorinated hydrocarbons since absorption is rapid, and visible clinical symptoms are quickly revealed (Lehman, 1951). Rapid uptake as well as a higher water solubility account for the narrow range between lowest toxic and lethal doses of γ-HCH relative to similar compounds like DDT (Gunther, et al. 1968; Martin, 1971).

A case of acute poisoning with γ-HCH in a 42-year-old male worker revealed an array of symptoms: depression, headache, emesis, asthemia, epileptiform attacks, sleeplessness, profuse perspiration, pathologically increased tendon reflex, tremor of the fingers, oral automatism, bilateral Marinesiu-Radovici reflex, Romberg's sign, and Hoffmann's and Troemmer's signs in the upper extremities. The blood contained γ-HCH between 0.1 and 0.5 ppm, and the cerebrospinal fluid contained 0.2 ppm γ-HCH several weeks after poisoning. This patient was therapeutically treated with barbituates, sedatives, glucose, and vitamins C and B12, which elicited a favorable response (Pernov and Kyurkchiyev, 1974).

Another case describes a 35-year-old man who ingested γ-HCH contaminated food. Grand mal seizures which recurred for nearly two hours, developed rapidly as well as severe acidemia. Muscle weakness and pain, headaches, episodic hypertension, myoglobinuria, acute renal failure and anemia were also experienced. Pancreatitis developed on the 13th day after ingestion, and on the 15th day, a muscle biopsy

revealed widespread necrosis and muscle fiber regeneration. Characteristic symptoms which occurred during the year following exposure included recent memory loss, loss of libido, and easy fatigability (Munk and Nantel, 1977). Topical application of γ-HCH in a child caused irritability and hyperactivity (Wheeler, 1977). Subsequent accidental oral administration of γ-HCH induced sporadic vomiting. Central nervous system stimulation seems to be the major toxic function of HCH, regardless of the absorption mechanism (Wheeler, 1977). This manifestation is of primary clinical importance. In most animals, initial symptoms of poisoning include an aggressive and excited state. Some cases of accidental acute γ-HCH poisoning in man by oral intake are shown in Table 1.

Alterations in liver function are also significant toxicological effects of HCH. Rats fed both the β and γ isomers showed an increase in alanine aminotransferase, and a decrease in aspartate aminotranferase, alkaline phosphatase, and acid phosphatase (Srinivasan and Radhakrishnamurty, 1977). After short-term oral administration of γ-HCH to rats, (5 to 20 mg/kg), an increase in the ascorbic acid in the urine and blood serum was noted. Electron microscopy revealed an increase in smooth endoplasmic reticulum in liver hepatocytes of the intermediary zone. Free ribosomal increase was probably related to the intensified formation of microsomal protein. Individual cell glycogen content was also observed and explained by increased glucuronic and ascorbic acid syntheses (Herbst, et al. 1974). Histochemical studies following daily administration of 7.5 mg

Table 1

Accidental acute γ-HCH poisoning in man
(oral intake)

Persons involved	Age	Dose (mg/kg)	Fatal cases	Formulation involved	Remarks
10	adults & children	up to 300	3	50 % WP	7 survived on therapy
1	adult	ca. 90	–	20 % EC	survived on therapy
11	adults	ca. 10	–	crystalline in coffee	survived on therapy
8	children	?	4	* highgrade BHC (?) (p.o. + p.c. + inhal.)	4 survived on therapy, all undernourished
1	child	(?) ca. 30	–	dust formulation	no symptoms
7	children	ca. 50-120	–	smoke sticks	survived on therapy
6	children	ca. 6- 80	–	smoke sticks	survived on therapy
3	children	up to 65	–	smoke sticks	survived on therapy
5	adults	?	4	in alcohol	1 survived on therapy
2	infants	?	2	smoke sticks	–
3	children	?	–	smoke tablets	survived on therapy
2	adults	?	1	20 % EC	survived on therapy
1	child	?	1	1/2 smoke tablet	–
1	child	?	–	10 % or 20 % EC	no therapy, severe after effects
5	adults	?	–	powder in pudding	survived on therapy
1	–	?	–	vermicide tablets	undernourished, survived on therapy
1	child	?	1	smoke tablet	–
1	child	?	–	?	survived on therapy
1	child	?	1	4–5 smoke tablets	–
1	child	?	1	1/2 smoke tablet	–
4	1 child, 3 adults	?	–	*1xinhalation, 4xp.o.	1 x urticaria, all survived on therapy
5	?	1 x 48 4 x ?	–	? ?	–
1	adult	152	–	crystalline, dust	survived on therapy
1	child	?	–	smoke tablets	survived on therapy

of the γ-isomer to albino rats revealed disturbances in the carbohydrate metabolism activation lytic processes (Shilina, 1973). High concentrations of the β-isomers have been detected in humans with various liver diseases. γ-HCH may also modify the metabolism of drugs in the liver (Vrochinskii, et al. 1976).

Dikshith, et al. (1978) gave daily dermal applications of HCH in 100, 200, and 500 mg/kg doses for 30 days. No mortality occurred in response to the 100 mg/kg/day, but significant pathologic and biochemical changes occurred in the vital organs. Massive congestion and thickened blood vessels were seen in the liver of the 100 mg HCH treated animals as compared to the controls. Biochemically, the activity of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and alkaline phosphatase in the liver and serum revealed significant changes from that of the controls. All animals exposed to the high doses (200 and 500 mg) died within 5 to 12 days.

Hexicid (1 percent γ-HCH) is highly effective in the treatment of scabies. Toxic side effects with irritation of the central nervous system have been reported after improper or prolonged use (Lee, et al. 1976). Side effects have included nausea, vomiting, spasms, weak respiration with cyanosis and blood dyscrasia. The absorption of γ-HCH has been shown to be in the order man < pig < rat < rabbit and the permeability characteristics of pig skin were closest to that of man (Bartek and LaBudde, 1975).

Extensive data regarding the chronic toxicity of γ-HCH to rats were revealed by several investigators in the early 1950's (Fitzhugh, et al. 1950; Lehman, 1952a,b). These studies involved the administration of γ-HCH in the crystalline form at 0, 10, 100, and 800 ppm, and as an oil solution at 0, 5, 10, 50, 100, 400, 800, and 1600 ppm. No clinical or pathological changes were detected at levels of 400 ppm or lower; however, liver weight increase was noticed at 100 ppm, particularly with respect to the oil forms. This was a dose-related effect and increased with concentration. At higher doses, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted. Oil solution concentrations of 400, 800, and 1600 ppm decreased lifespan by 20 to 40 percent, although a concentration of 800 ppm crystalline form did not yield similar effects.

Inhaled administration of γ-HCH to rats with varying exposure times resulted in little or no organ alterations. Inhalations of 0.78 mg/m^3 for seven hours, five days a week for 180 days did show some liver cell enlargement although no clinical symptoms were noticed. Rats exposed to three percent γ-HCH dust for seven hours a day, five times a week for 218 days revealed some doubtful liver and kidney changes in two of 20 animals exposed (Heyroth, 1952). In 1954, the United States and most western countries, as a result of these and other inhalation experiments, established a maximum allowable concentration of 0.5 mg/m^3 (Ball, 1956).

The addition of γ-HCH at 10 ppm to the diet of rats for one to two years revealed noxious effects to them and their offspring. Body weight decreased after five months of administration, and increased ascorbic acid levels in the urine along with variable modification of the content in the blood were noted. Ascorbic acid was decreased in both the liver and adrenals (Petrescu, et al. 1974). Experimental data regarding the toxicity of various isomers of HCH are shown in Table 2.

Male and female beagle dogs were fed γ-HCH in the diet at concentrations of 25, 50, and 100 for 104 weeks. Friable and slightly enlarged livers were noted at 100 ppm, but no histopathological changes were noticed. The negative findings at 50 ppm are consistent with a no-effect level for this species (Rivett, et al. 1978). The no-effect levels after chronic poisoning to several other mammals are shown in Table 2.

Kazakevich (1974) has reported that production workers with exposure to t-HCH have exhibited a variety of symptoms including headache, vertigo, irritation of the skin, eyes and respiratory tract mucosa, etc. In some instances, there were apparent disturbances of carbohydrate and lipid metabolism. Dysfunction of the hypothalamo-pituitary-adrenal system was also reported by the authors. Besughyi, et al. (1973) reported similar findings in 88 persons having headache, vertigo, and irritation of the skin, eyes and respiratory tract mucosa.

TABLE 2

Toxicity of HCH Isomers

Chemical Form and Animal Species	Duration of Study	Dosage Levels and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat					
t-HCH	approx. 2 yr	10, 50, 100, 800 ppm (10 M, 10 F)	800 ppm	reduced lifespan, no	Fitzhugh, et al.
α-HCH, -HCH	approx. 2 yr	10, 50, 100, 800 ppm (10 M, 10 F)	800 ppm	increased tumor in-	1950
γ-HCH	approx. 2 yr	5, 10, 50, 100, 400, 800, 1,600 ppm (10 M, 10 F)	800 ppm	cidence	
γ-HCH	2 yr	25, 50, 100 ppm	100 ppm	no increase in tumor incidence	Truhant, 1954
α-HCH	78 weeks	500, 1,000, 1,500 ppm (18-24 M)	500 ppm	liver hypertrophy (nodular hyperplasia, carcinoma at 1,000 and 1,500 ppm)	Ito, et al. 1975
β-HCH	78 weeks	500, 1,000 ppm	500 ppm	liver hypertrophy	
γ-HCH	78 weeks	500 ppm	500 ppm	liver hypertrophy	
δ-HCH	78 weeks	500, 1,000 ppm	1,000 ppm	liver hypertrophy	
Mouse					
t-HCH	24 weeks	6.6, 66, 660 ppm (20 M, dd strain)	660 ppm	hepatoma (20/20)	Nagasaki, et al. 1971, 1972a
α-HCH	24 weeks	100, 250, 500 ppm (20 M, dd strain)	250 ppm	hepatic nodules (9/20), tumors at 500 (20/20)	Nagasaki, et al. 1972b
β-HCH	24 weeks	100, 250, 500 (20 M, dd strain)	500 ppm	no adverse effect	
γ-HCH	24 weeks	100, 250, 500 (20 M, dd strain)	500 ppm	no adverse effect	
β-HCH	110 weeks	200 ppm (30 M, 30 F; CFI strain)	200 ppm	hepatic tumors, lung metastases	Thorpe and Walker, 1975
δ-HCH	110 weeks	400 ppm (29 M, 29 F; CFI strain)	400 ppm	hepatic tumors, lung metastases	
t-HCH	26 weeks	600 ppm (20 M; ICR-JCL strain)	600 ppm	hepatic nodules, tumors	Goto, et al.
α-HCH	26 weeks	600 ppm (20 M; ICR-JCL strain)	600 ppm	hepatic tumors, lung metastases	1972
β-HCH	26 weeks	600 ppm (20 M; ICR-JCL strain)	600 ppm	hepatic tumors, lung metastases	
δ-HCH	26 weeks	600 ppm (20 M; ICR-JCL strain)	600 ppm	hepatic tumors, lung metastases	
γ-HCH	26 weeks	300, 600 ppm	300 ppm	no adverse effect	
α-HCH	24 weeks	50, 100, 250, ppm (30 M, dd strain)	100 ppm	liver hypertrophy (hyper-	Ito, et al.
β-HCH	24 weeks	50, 100, 250 ppm (30 M, dd strain)	250 ppm	plasia, tumors at 250) liver hypertrophy	1975
γ-HCH	24 weeks	50, 100, 250 ppm (30 M, dd strain)	250 ppm	liver hypertrophy (slight)	
γ-HCH	80 weeks	12.5, 25, 50 ppm (NMRI strain)	50 ppm	no adverse effect	Herbst, et al. 1975

These compounds are animal carcinogens. (adapted from NAS, 1977)

A study involving 59 females and 29 males with occupational exposure to HCH for periods ranging from 11 to 23 years revealed biochemical manifestations of toxic hepatitis. Fifty-five percent of the workers showed pathological changes in the hepatobiliary system, 33 percent of the total being chronic hepatitis, and 5 percent being chronic pancreatitis. Some form of biochemical abnormality was noted in 60 percent of all cases (Sasinovich, et al. 1974).

Synergism and/or Antagonism

The daily pretreatment of beagle dogs with phenobarbital for 60 days prior to the administration of γ-HCH brought about a reduction of γ-HCH concentrations in the brain. The control dogs (without pretreatment) were found to convulse after 27 minutes of I.V. infusion of 7.5 mg γ-HCH/minute, while the phenobarbital-pretreated group did not convulse within 60 to 70 minutes. By the end of the infusion period, the phenobarbital pretreated group showed significantly higher concentration of blood γ-HCH. As compared with the control group, the brains of the phenobarbital pretreated group contained a much smaller amount of the total γ-HCH administered. It seems that phenobarbital pretreatment leads to decreased convulsion effect of γ-HCH (Litterst and Miller, 1975).

Various substances have been found to have antagonistic effects on γ-HCH poisoning and offer potential as treatment or antidotes. The administration of silymarin to γ-HCH-intoxicated mice resulted in a prolonged survival time (Szpunar, et al. 1976). An oral application mixture of HCH and Rogor at concentrations of 3.2 and 3.8 mg/kg body weight to rabbits

for a three month period resulted in disruption of lipid metabolism and a decreased serum cholesterol/lecithin ratio. However, methionine, galascorbin, and vitamin B12, individually aided the recovery of disrupted lipid metabolism, although a combination of the three was more effective (Karimov, 1976). Alterations in the serum cholestrol levels may be indicative of chronic poisoning by these pesticides.

Pretreatment of Wistar rats with γ-HCH has revealed a reduction in the teratogenic effect of some compounds. Preliminary treatment weakened the teratogenic and embryotoxic action of the carbamate insecticide given in a dose of 400 mg/kg and of sodium acetylsalicylate administered in a dose of 400 mg/kg (Shtenberg and Torchinskii, 1977).

The chlorination of water containing various organochlorine pesticides, including HCH, decreases the LD50 level of mice and rats by conversion of the compounds to more toxic products. This effect was determined by changes in blood erythrocytes, enzymes, and -SH levels, disruption of protein synthesis by the liver, and a decreased rate of weight gain (Shtannikov, et al. 1977).

γ-HCH has also showed to be synergistic or antagonistic with other substances. The sensitivity of mice to pentylenetetrazol at concentrations of 1, 3, 4, 6, and 12 mg/kg body weight was increased by pretreatment of γ-HCH at 10, 7.5, 5, 2.5, and 1.2 mg/kg body weight. The results showed a significantly higher frequency of convulsions than expected from pentylenetetrazol alone. Therefore, the convulsive dose threshold is lowered by small, single oral doses of γ-HCH in the mouse (Hulth, et al. 1976). γ-HCH administered

in sublethal doses to rabbits resulted in immunosuppression of antibody formation in response to Salmonella typhi injections (Desi, 1976).

The toxic effects of γ-HCH have also been antagonized by various tranquilizers (Ulmann, 1972).

Teratogenicity

A study regarding the potential teratogenic effects of γ-HCH involved the p.o. administration in a vegetable oil solution in 4 groups of rats. Groups 1 through 3 were fed 25 mg. γ-HCH/kg body weight/day while Group 4 was fed 12 mg γ-HCH/kg body weight/day. Group numbers 1 and 4 received γ-HCH throughout pregnancy (days 1 to 20), while Group 2 received lindane throughout placentation and orogenesis (days 7 to 15) and Group 3 during preimplantation period (days 1 to 7). All animals were sacrificed on day 20 and examined. No teratogenic effects were noticed in any of the experimental groups. Females in Group 1 did show, however, increased postimplantation death of embryos: 25.6 percent compared with 11.2 percent in Group 2, 7.6 percent in Group 3, and 9.5 percent in Group 4, and 13.2 percent in nontreated controls (Mametkuliev, 1978). Similar results were obtained by Palmer, et al. (1978) with white rabbits. The effects of lindane on reproductive capacity were examined by Petrescu, et al. (1974). Four generations of rats (327 animals total) were studied. The investigators reported that 5, 10, or 15 mg/kg body weight administered in the diet resulted in an increase in the average duration of pregnancy from 21 to 22 days in the control animals to 21 to 24 days in the lindane-fed animals. Also, the dosage 15 mg/kg decreased

the number of births compared to the number of animals in the parental generation. Numbers fell from 100 births per control parental population to 60 births in lindane-fed animals per parental population. Also noted were delayed opening of the vagina, delayed initiation of first estrous in offspring of experimental groups, and longer estrous cycles in F2 and F3 generations. These results are indicative of altered sexual maturation and function and suggest that exposure to lindane during pregnancy causes reduced reproductive capacity in parents and subsequent generations. An increase in the proportion of stillbirths with succeeding generations of lindane-fed animals was also noted in this study:

Generation	Number of Stillbirths	
	Control	5, 10, 15 mg/kg
F_1	0/50	1/104
F_2	1/45	25/64
F_3	0/56	3/6

In addition, F_1 and F_2 animals of the lindane-fed group exhibited spastic paraplegia, 17/119 and 7/52, respectively.

Mutagenicity

Male mice were administered single intraperitoneal doses of 12.5, 25, and 50 mg γ-HCH/kg (1/8, 1/4, and 1/2 of the LD50) and later mated with females during a seven day period. No mutations or reproductive effects were noted (cited in U.S. EPA, 1973). Mutagenic rates too low to be considered positive were found in host-mediated testing (Buselmair, et al. 1973). Some alterations in mitotic activity

and the karyotype of human lymphocytes cultivated *in vitro* with γ-HCH at concentrations between 0.1 and 10.0 mg/ml have been reported by Tsoneva-Maneva, et al. (1971).

Carcinogenicity

Experimentation with γ-HCH in the early 1950's yielded little or no data in support of carcinogenic activity. Accumulation of epidemiological data (Hans, 1976), however, initiated more recent investigations into the potential carcinogenic action of HCH. This shift was also prompted by an increase in agricultural use of HCH in Japan. One case report of a Japanese sanitation employee revealed acute leukemia which apparently was associated with occupational exposure to the insecticides HCH and DDT. It was believed that the 44-year-old patient had inhaled the chemicals for eight years of his employment, never having worn protective face masking. The diagnosis on autopsy was acute leukemia with hypoplastic marrow and hemosiderosis. The author speculates that the absorption of DDT and t-HCH via the alveoli led to aplastic anemia, which was then probably transformed into leukemia (Hoshizaki, et al. 1970).

When γ-HCH was administered orally at 800 ppm and more to rats tumor incidence was not greater than controls, although average life spans were reduced (Fitzhugh, et al. 1950). It is important to note, however, that all organs were not microscopically examined. Truhant (1954) supported these findings by feeding diets containing γ-HCH at 25,

50, or 100 ppm to rats for two years. Again, no significant increase in tumors was observed.

Nagasaki (1972a) reported the development of liver tumors in all male mice which were fed 660 ppm dietary t-HCH for 24 weeks. 66.0 and 6.6 ppm did not induce tumors but did increase liver weights. The 66.0 ppm dietary level also revealed some cellular hyperplasia. Excessive amounts of α and β-HCH accumulated in the liver at the 660 ppm level. γ and δ-HCH were found only in trace amounts.

A later experiment involved feeding the α, β, γ, and δ isomers separately at levels of 100, 250, and 500 ppm. After 24 weeks the experiment was terminated and revealed multiple liver tumors as large as 2.0 centimeters in diameter in all animals given α-HCH at the 500 ppm level. The 250 ppm α-HCH level resulted in smaller nodules, while no lesions were found in mice fed 100 ppm. The various dosages did not produce any tumors with respect to the other isomers, (Nagasaki, et al. 1972b). Pathomorphological investigations by Didenko, et al. (1973) established that the γ isomer did not induce tumors in mice given intragastric administration at doses of 25 mg/kg twice a week for five weeks.

Hanada, et al. (1973) fed six-week-old mice a basal diet of 100, 300, and 600 ppm t-HCH and the α, β, γ isomers for a period of 32 weeks. After 38 weeks, liver tumors were found in 76.5 percent of the males and 43.5 percent of the females fed t-HCH indicating that males were more highly susceptible to HCH induced tumors than females.

Multiple nodules were found in the liver, although no peritoneal invasion or distinct metastasis was found. The β-isomer-treated animals had no tumors.

Goto, et al. (1972) reported on feeding eight groups of five-week-old male mice of the ICR-JCL strain diets containing 600 ppm of the following compounds: Group 1, t-HCH; Group 2, α-HCH; Group 3, β-HCH; Group 4, γ-HCH; Group 5, a mixture of δ-HCH and ε-HCH; Group 6, 1,2,4-trichlorobenzene; Group 7, 2,3,5-trichlorophenol; Group 8, 2,4,5-trichlorophenol. A 9th group received 300 ppm γ-HCH. After 26 weeks, no increase in weight of the heart, liver, and kidneys was noticed for Groups 6 to 9; however, a marked increase in liver weight was noticed in mice of Groups 1 to 5.

Macroscopic examination of the livers revealed tumors in all mice of Groups 1 and 2; eight of ten mice in Group 5; and five of ten mice in Group 4.

The results of these experiments offer support that t-HCH and α-HCH frequently cause malignant liver tumors in mice subjected to oral administration of high doses (600 ppm) for six months. The same experimental conditions involving β-HCH or γ-HCH produced benign tumors. Malignant tumors were also produced in mice of Group 5, although it was not established whether δ, ε, or the mixture was responsible for the hepatomas.

The combination of β-, γ-, or δ-HCH with the highly carcinogenic action of α-HCH revealed no synergistic or antagonistic effect on the production of tumors by α-HCH for dd strains of mice (Ito, et al. 1973). Proliferation

of cytoplasmic endoplasmic reticulum as well as nuclear and mitochondrial changes were noticed in the region of hepatocellular carcinomas.

The feeding of mice 500 ppm α-HCH for a 24-week period resulted in nodular hyperplasias of the liver (Sugihara, et al. 1975). These nodules began to disappear after discontinuation of the compound, but after 24 more weeks, hepatocarcinomas developed. At the end of initial administration, the ultrastructure of the nodular cells was characterized by large, oval shaped nuclei with clear nucleoplasm. Four weeks after discontinuation, active phagocytotic processes appeared between nodular cells. Although the number of nodular cells decreased after cessation of poisoning, the ones remaining after 12 weeks showed tumorous growth. Apparently, the remaining nodular cells are responsible for the development of the hepatocellular carcinomas (Sugihara, et al. 1975).

Some contradiction appears in the literature with respect to the carcinogenic action of the γ-HCH isomer. Thorpe and Walker (1973) noticed tumorigenic action caused by the γ-isomer in the CF1 strain mice. However, the dose administered in this experiment of 400 ppm γ-HCH may be higher than the maximum tolerated dose. Associated liver enlargement and hepatomas may have also resulted from non-specific toxic effects, since only 3 percent of the females and 17 percent of the males fed γ-HCH survived the duration of the experiment. Additionally, the administered dose was 70 percent of the acute oral LD_{50}.

The National Cancer Institute conducted a bioassay for the possible carcinogenicity of γ-HCH to Osborne-Mendel rats and B6C3F1 mice. Administration continued for 80 weeks at 2 dose levels: time-weighted average dose for male rats was 236 and 472 ppm; for female rats, 135 and 270 ppm; and for all mice, 80 and 160 ppm. No statistically significant incidence of tumor occurrence was noted in any of the experimental rats as compared to the controls. At the lower dose concentration in male mice, the incidence of hepatocellular carcinoma was significant when compared to the controls, but not significant in the higher dose males. "Thus, the incidence of hepatocellular carcinoma in male mice cannot clearly be related to treatment." The incidence of hepatocellular carcinoma among female mice was not significant. Consequently, the carcinogenic activity of γ-HCH in mice is questionable (Natl. Cancer Inst., 1977).

Experiments by Nagasaki, et al. (1972a,b) with other strains produced negative results. According to Miura, et al. (1974), the toxicity of t-HCH and HCH isomers varies significantly among different strains of mice, with the CF1 strain being particularly susceptible. Feeding 500 mice of the Chbi:NMRI(SPF) strain γ-HCH at levels of 12.5, 25, and 50 ppm in the food for 80 weeks revealed no compound-induced lymphatic leukemia, no malignant hemangioendotheliomas, and no liver cell adenomas (Herbst, et al. 1975). Electron-microscopical examinations of SPF mice which were fed the same concentrations, provided no evidence of γ-HCH-induced fine structural hepatocellular alterations (Weisse and Herbst, 1977).

In a study by Ito, et al. (1975) male Wistar-derived rats were fed several isomers of HCH in the diet for 72 weeks. The α-HCH isomer was administered at 500, 1000, and 1500 ppm, β-HCH at 500 and 1000 ppm, γ-HCH at 500 ppm and δ-HCH at 500 and 1000 ppm. The 500 ppm level of all isomers produced no neoplastic changes, cell infiltration, fatty changes, fibrosis, or bile duct proliferation, but liver weights did increase in all groups except the -HCH treated rats. Only the α-HCH-treated group revealed tumor development. No metastasis were seen and no tumorous growths developed in any of the other dietary groups (Ito, et al. 1975).

One instance of carcinogenic synergism of γ-HCH in combination with leupeptin showed a fivefold increase in hepatic nodular hyperplasia (Arai, et al. 1978). Other experiments have shown γ-HCH to have an antagonistic effect on the hepatocellular carcinoma induction by aflatoxin B1 in male albino rats (Angsubhakorn, et al. 1978).

No data are currently available in the scientific literature on the carcinogenicity of the δ and the ϵ isomers of HCH. Furthermore, the δ and ϵ isomers are rarely detected in the environment.

CRITERION FORMULATION

Existing Guidelines and Standards

The FAO/WHO Allowable Daily Intake (ADI) is set at 1 µg/kg/day and was revised down to that figure from 12.5 mg/kg/day originally set by FAO/WHO in 1972. Barney (1969) showed the average daily intake of HCH for U.S. citizens to be 0.002 µg/kg/day from the air and 0.07 µg/kg/day for foodstuffs, clearly below the established level of 1 µg/kg/day.

The EPA set the tolerance for animal fats at 7 ppm, and 0.3 ppm for milk. One ppm is the tolerance level for most fruits and vegetables. Finished drinking water should contain no more than 0.004 ppm. The maximum air concentration that is allowed by the EPA is 0.5 mg/m^3 of air. Cases of HCH poisoning in Japan have shown concentrations of 23 and 59 mg/m^3 at factories involved in the manufacture of HCH. In both cases a number of workers became ill with convulsions. It is clear that research is needed concerning the effects of long term, low level air concentrations of the HCH isomers.

Current Levels of Exposure

Considering the steady decline in the use of organochlorine insecticides, it is likely that HCH concentrations will continue to fall. This should also lower the amount of human exposure of HCH by oral ingestion. Dermal and inhalation, however, are recognized sources of contamination for those involved in the manufacture, use, and formulation of HCH and its isomers.

There is considerable pressure in the European countries to ban all organochlorine insecticides except lindane (γ-HCH). It is strongly believed by many that γ-HCH does

not represent a pollution problem. It is recognized by the same scientists that α and β-HCH do represent a significant hygienic problem. α and β-HCH are accumulated up the food chain, e.g., Japanese rice ⟶ rice straw ⟶ cattle ⟶ cattle products ⟶ man. t-HCH contains a significant amount of the α and β-isomers, so production of t-HCH should be restricted and only production of γ-HCH allowed. The presence of the α and β-isomers has in part given rise to the hypothesis that the γ-isomer can be transformed to the unwanted isomers. Experimental isomerization has occurred (Newland, et al. 1969), but only under anaerobic aquatic conditions and probably by microorganisms. There is a lack of bioisomerization in mammals. It should not be overlooked that α-HCH, despite its relatively short half-life, will be detected for a long time following the use of t-HCH, in which it is present in high proportion (60 to 70 percent). Practical proof of this theory is shown by the fact that in countries where the use of t-HCH was terminated (and no γ-HCH had been used), residues of α and β-HCH were found for many years. It is known that in such cases, the relative share of β-HCH of the total HCH residues is going up. If γ-HCH is used exclusively in an area, then the share of γ-HCH of the total HCH residues will vary in accordance with the extent of application, and the other isomers will show a downward trend.

Special Groups at Risk

No t-HCH or γ-HCH is currently manufactured in the U.S. Use of t-HCH has been banned but γ-HCH is still approved for usage. All γ-HCH used in the U.S. is currently imported;

there is no exposure during manufacture in this country. Formulators, distributors and users of the product certainly represent a special risk group. The major use of γ-HCH in recent years has been to pretreat seeds (42 percent in 1974), representing a source of exposure for employees of the seed companies. Agricultural workers could be exposed during handling and planting of the seed and during application to crops.

Basis and Derivation of Criterion

The animal carcinogenicity data from Ito, et al. 1976, Goto, et al. 1972, Thorpe and Walker, 1973, and Nagasaki, et al. 1972a have been used to develop water quality criteria for α, β, γ, and technical HCH, respectively. These criteria have been developed by the Carcinogens Assessment Group of EPA. The assessment is given in Appendix I.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." α-HCH, β-HCH, γ-HCH and t-HCH are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of α-HCH, β-HCH, γ-HCH and t-HCH in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of -HCH, -HCH, -HCH and t-HCH corresponding to several incremental lifetime

cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the tables below.

α-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.16 ng/l	1.6 ng/l	16 ng/l
Consumption of fish and shellfish only.	0	0.18 ng/l	1.8 ng/l	18 ng/l

β-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.(2)	0	0.28 ng/l	2.8 ng/l	28 ng/l
Consumption of fish and shellfish only.	0	0.32 ng/l	3.2 ng/l	32 mg/l

-HCH

Exposure Assumptions	Risk Levels and Corresponding Criteria[1]			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0	0.54 ng/l	5.4 ng/l	54 ng/l
Consumption of fish and shellfish only.	0	0.61 ng/l	6.1 ng/l	61 ng/l

-HCH

Exposure Assumptions	Risk Levels and Corresponding Criteria[1]			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0	0.21 ng/l	2.1 ng/l	21 ng/l
Consumption of fish and shellfish only.	0	0.24 ng/l	2.4 ng/l	24 ng/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the FR15926, 1979. Appropriate bioassay data used in the calculation of the model are presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1000, and so forth.

(2) Approximately 88 percent of the α-HCH, β-HCH, γ-HCH and t-HCH exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 780 fold. The remaining 12 percent of α-HCH, β-HCH, γ-HCH and t-HCH exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of HCH (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding HCH concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding HCH concentrations. Although total exposure information for HCH is discussed and an estimate of the contributions from other sources of exposure can be made, these data will not be factored into ambient water quality criteria formulation until additional analyses can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

Water quality criteria for the δ and ϵ isomers of HCH have not been established because of insufficient data. These isomers have not been dectected in the environment, however, and would not appear to be a health risk. In summary, the recommended water quality criteria for hexachlorocyclohexane is as follows:

Form	Criteria
α isomer	16 ng/l*
β isomer	28 ng/l*
γ isomer	54 ng/l*
δ isomer	not established-insufficient data
ϵ isomer	not established-insufficient data
technical	21 ng/l

*At a risk level of one in 100,000.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Hexachlorocyclohexane

Hexachlorocyclohexane (HCH;BHC) is a saturated chlorinated hydrocarbon which has insecticidal properties. Technical grade HCH is composed of five basic isomers including the alpha (α), beta (β), gamma (γ), delta (δ), and epsilon (ε) isomers. The gamma isomer (gamma-HCH; γ-BHC; Lindane) has the lowest melting point (112°C) and also has the highest acute toxicity of these five isomers of HCH.

So far, 2,4,6-trichlorophenol is the only metabolite of gamma-HCH shown to be an animal carcinogen (National Cancer Institute, 1979).

Reports concerning the mutagenicity of hexachlorocyclohexane relate to the gamma isomer. Although gamma-HCH was found to be mutagenic in microbial tests using Salmonella typhimurium TA 1535 and TA 1538 with metabolic activation (Ames test), the host-mediated assay and the dominant lethal test in rats, other reports indicate that it does not have significant mutagenic activity.

Numerous reports concerning the carcinogenicity of technical hexachlorocyclohexane and its isomers are in the literature. An increased incidence of liver tumors was reported in mael and/or female mice of various strains fed technical HCH (Goto, et al. 1972; Hanada et al. 1973; Nagasaki, et al. 1972a), alpha-HCH (Goto, et al. 1972; Hanada, et al. 1973; Ito, et al. 1973; Ito, et al. 1976; Nagasaki, et al. 1972b; Nagasaki, et al. 1975), beta-HCH (Goto, et

al. 1972; Thorpe and Walker, 1973) and gamma-HCH (Goto, et al. 1972; Hanada, et al. 1973; National Cancer Institute, 1977; Thorpe and Walker, 1973). Male rats fed alpha-HCH for up to 72 weeks also developed liver tumors (Ito, et al. 1975). One report in the literature (Goto, et al. 1972) detailed an increase of liver tumors in mice fed a mixture of delta and epsilon isomers of HCH, but there were no studies which used individual delta or epsilon isomers.

The induction of liver tumors in male and female mice from the administration of either technical HCH, alpha-HCH, beta-HCH, or gamma-HCH and the induction of liver tumors in male rats from the administration of alpha-HCH indicates that technical, alpha-, beta-, and gamma-HCH are likely to be human carcinogens.

The water quality criterion for technical HCH is based on the induction of liver tumors in male dd mice fed 660 ppm technical hexachlorocyclohexane for 24 weeks (Nagasaki, et al. 1972a). It is concluded that the water concentration of technical HCH should be less than 21 nanograms per liter in order to keep the lifetime cancer risk below 10^{-5}.

The water quality criterion for alpha-HCH is based on the induction of liver tumors in male DDY mice fed 500 ppm alpha-hexachlorocyclohexane for 24 weeks (Ito, et al. 1976). It is concluded that the water concentration of alpha-HCH should be less than 16 nanograms per liter to keep the lifetime risk below 10^{-5}.

The water quality criterion for beta-HCH is based on the induction of liver tumors in male ICR-JCL mice fed 600 ppm beta-hexachlorocyclohexane for 26 weeks (Goto, et al. 1972). It is concluded that the water concentration of beta-HCH should be less than 28 nanograms per liter in order to keep the lifetime risk below 10^{-5}.

The water quality criterion for gamma-HCH is based on the induction of liver tumors in male CF1 mice fed 400 ppm gamma-hexachlorocyclohexane for 110 weeks (Thorpe and Walker, 1973). It is concluded that a water concentration of gamma-HCH should be less than 54 nanograms per liter in order to keep the lifetime cancer risk below 10^{-5}.

Because of insufficient data, a water quality criterion cannot be established for either the delta or epsilon isomer of hexachlorocyclohexane.

Summary of Pertinent Data

The water quality criterion of alpha-hexachlorochyclohexane is derived from the oncogenic effects observed in the liver of male DDY mice fed 500 ppm alpha-HCH in the diet (Ito, et al. 1976). The time-weighted average dose of 65 mg/kg/day was given in the feed for 24 weeks. The liver tumor incidence was 0/18 and 20/20 in the control and treated groups, respectively. Assuming a fish bioconcentration factor of 780, the criterion is calculated from the following parameters:

n_t = 20 (used 19.5 for calculation)

N_t = 20

n_c = 0

N_c = 18

le = 24 weeks

Le = 90 weeks

d = 500 ppm X 0.13 = 65 mg/kg/day

R = 780

L = 90 weeks

w = 0.0357 kg

F = 0.0187 kg/day

Based on these parameters, the one-hit slope, BH, is 2.6637. The resulting water concentration of alpha-hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 16 nanograms per liter.

Summary of Pertinent Data

The water quality criterion for beta-hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male ICR-JCL mice fed 600 ppm beta-HCH in the diet (Goto, et al. 1972). The time weighted average dose of 78 mg/kg/day was given in the feed for 26 weeks. The liver tumor incidence was 0/10 and 10/10 in the control and treated groups, respectively. Assuming a fish bioconcentration factor 780, the criterion is calculated from the following parameters:

n_t = 10 (used 9.5 for calcuation)	d = 600 ppm X 0.13 = 78 mg/kg/day
N_t = 10	R = 780
n_c = 0	L = 90 weeks
N_c = 10	w = 0.0475 kg
le = 26 weeks	F = 0.0187 kg/day
Le = 90 weeks	

Based on these parameters, the one-hit slope, B_H is 1.5129. The resulting water concentration of beta hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 28 nanograms per liter.

Summary of Pertinent Data

The water quality criterion for gamma-hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male CF1 mice fed 400 ppm gamma-HCH in the diet (Thorpe and Walker, 1973). The time-weighted average dose of 52 mg/kg/day was given in the feed for 110 weeks. The liver tumor incidence was 11/45 and 27/28 in the control and treated groups, respectively. Assuming a fish bioconcentration factor of 780, the criterion is calculated from the following parameters:

n_t = 27	d = 400 ppm x 0.13 = 52 mg/kg/day
N_t = 28	R = 780
n_c = 11	L = 110 weeks
N_c = 45	w = 0.030 kg
le = 110 weeks	F = 0.0187 kg/day
Le = 110 weeks	

Based on these parameters, the one-hit slope, B_H, is 7.7844×10^{-1}. The resulting concentration of gamma-hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 54 nanograms per liter.

Summary of Pertinent Data

The water quality criterion for technical hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male dd mice fed 660 ppm technical HCH in the diet (Nagasaki, et al. 1972a). The time-weighted average dose of 85.8 mg/kg/day was given in the feed for 24 weeks. The liver tumor incidnce was 0/14 and 20/20 in the control and treated groups, respectively. Assuming a fish bioconcentration factor of 780, the criterion is calculated from the following parameters:

n_t = 20 (used 19.5 for calculation)	d = 660 ppm x 0.13 = 85.8 mg/kg/day
N_t = 20	R = 780
n_c = 0	L = 90 weeks
N_c = 14	w = 0.0364 kg
le = 24 weeks	F = 0.0187 kg/da
Le = 90 weeks	

Based on these parameters, the one-hit slope, B_H is 2.0050. The resulting water concentration of technical hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 21 nanograms per liter.